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The need for *Helicobacter pylori* eradication therapy in patients with peptic ulcer bleeding

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Peptic ulcer bleeding is an important complication of peptic ulceration. The condition carries significant morbidity and mortality despite advances in both endoscopic intervention techniques and pharmacological treatment. About one third of patients have a recurrence of bleeding within a few years of discharge. Before *Helicobacter pylori* was discovered, most of these patients were given maintenance therapy with antisecretory drugs or surgery to prevent a recurrence of the bleeding. Since the eradication of *Helicobacter pylori* reduces the recurrence of uncomplicated peptic ulcers, its eradication should also reduce peptic ulcer complications. The aim of this review is to discuss the value of eradicating *Helicobacter pylori* as part of the long-term management of bleeding peptic ulcers.

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Key words: *Helicobacter* infections; *Helicobacter pylori*; Peptic ulcer hemorrhage

Introduction

Bleeding is the most frequent complication of peptic ulcer disease, occurring in 20% of patients with ulcers^{1,2} and is a common cause of emergency hospital admission. Despite the introduction of endoscopic haemostatic methods and improvements in acid-suppressive drugs, peptic ulcer bleeding remains a life-threatening condition that carries a 5% to 10% mortality rate.³⁻⁷

It is now well accepted that *Helicobacter pylori* is the cause of type B gastritis and most peptic ulcers. There is considerable evidence that eradication of the organism markedly alters the natural history of uncomplicated peptic ulcer disease and reduces the recurrence of peptic ulceration.⁸⁻¹¹ More information on the relationship between *H pylori* and bleeding peptic ulcers is now available.

The prevalence of *H pylori* infection

Helicobacter pylori has been detected in almost 100% of patients with duodenal ulcers and in approximately 75% of those with gastric ulcers.¹² The prevalence of *H pylori* is, however, lower in patients with complicated

peptic ulcer diseases. For example, in patients presenting with perforated peptic ulcer, the prevalence of *H pylori* can be as low as 50%.¹³ Similarly, studies have found that 70% to 85% of patients with bleeding peptic ulcers have evidence of *H pylori* infection.¹⁴⁻¹⁶

The lower prevalence of *H pylori* in those with bleeding peptic ulcers means that factors other than *H pylori* are also important in the pathogenesis of bleeding peptic ulcers. The use of non-steroidal anti-inflammatory drugs (NSAIDs) is another important factor in the development of bleeding peptic ulcers. The use of NSAIDs has been found to be the most common cause of duodenal and gastric ulceration among patients who test negative for *H pylori*.¹⁷ Yet, up to 10% of a series of patients with bleeding peptic ulcers who were not NSAID users have been shown to be free of *H pylori* infection.¹⁸

The lower prevalence of *H pylori* observed in patients with bleeding peptic ulcers could also be due to the varying sensitivity and specificity of the *H pylori* diagnostic tests used in different studies. For example, results from the urease test on antral biopsy samples have been found to have a high false-negative rate for *H pylori* in patients with bleeding duodenal ulcers.^{19,20}

Interaction of *H pylori* and non-steroidal anti-inflammatory drugs

Since both *H pylori* infection and the use of NSAIDs are the most common causes of peptic ulceration, it

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is important to determine whether *H pylori* infection increases the risk of peptic ulceration in patients who are taking NSAIDs. Unfortunately, endoscopic and epidemiological studies of patients with uncomplicated peptic ulceration give conflicting results as to whether or not *H pylori* infection increases the risk of ulceration in NSAID users. The results from studies of patients with bleeding peptic ulcers are also conflicting. Two case-control studies failed to demonstrate any significant interaction between NSAIDs and *H pylori* in bleeding peptic ulcers,^{21,22} while a third case-control study concluded that *H pylori* infection is associated with an increase in the risk for bleeding peptic ulcers among NSAID users.²³

In contrast, it is well known that a prior history of ulcer disease is an important risk factor for the development of ulcer complications in patients who are taking NSAIDs^{24,25} and that these complications develop within 1 month of commencing NSAID therapy.^{26,27} These findings suggest that NSAIDs may cause complications in ulcers that are present but clinically silent. Patients who have *H pylori*-associated ulcers thus seem to have a greater risk of developing complicated ulcers during treatment with NSAIDs.

Diagnosing *H pylori* infection

Diagnostic tests to detect *H pylori* may be classified as those that require endoscopic gastric mucosal biopsies and those that do not require endoscopy and hence are non-invasive. Biopsy-based tests include gastric mucosal culture, histological examination, and the rapid urease test (RUT). Non-biopsy-based tests include the urea breath test and serological analysis.

Gastric mucosal culture remains the gold standard for detecting *H pylori* and is particularly useful for patients in whom eradication therapy has failed or for participants of clinical trials in which antibiotic resistance needs to be determined. However, culturing

for *H pylori* is generally not used for the diagnosis of infection because of the lower sensitivity when compared with other tests. In contrast, histological examination can detect gastritis as well as the presence of *H pylori*, and the test generally has a good sensitivity and specificity. Pitfalls that are related to sampling error, observer error, staining methods, and density of *H pylori* can occur, however.

The RUT is the most commonly used initial endoscopic test to diagnose *H pylori* infection owing to its simplicity, accuracy, and relatively rapid results. The RUT is based on the potent urease-producing activity of *H pylori*; the results are thus available within 1 to 24 hours. In contrast, the urea breath test is a non-invasive, non-endoscopic test that also employs the potent urease activity of the bacterium. Patients are required to drink a solution of urea labelled with carbon 13 or 14. Breath samples are collected before and 30 minutes after the administration of the labelled urea solution. The proportion of exhaled ¹³C or ¹⁴C is then calculated. The sensitivity and specificity of the urea breath test are very good. However, the analysis of ¹³C levels requires an expensive mass spectrometer, and ¹⁴C is radioactive and hence not suitable for use in repeated examinations.

Serological analysis depends on the presence of serum antibodies against *H pylori*. The test is not usually used to diagnose infection with the bacterium because the results may indicate a prior rather than a current infection.

Since none of the above tests are perfect, it is prudent to have two diagnostic tests performed to confirm the presence of *H pylori*. This precaution is particularly important when there are bleeding peptic ulcers. Results from the RUT have been found to have high false-negative rates in the presence of bleeding duodenal ulcers,^{19,20,28,29} which may be related to the presence of blood in the stomach. Biopsy-based

Table 1. *H pylori* infection and rebleeding in patients with and without eradication therapy

Study	Study design	Length of follow-up (months)	Ulcer type
Graham et al, ³⁴ 1993	Non-randomised	12	GU [†] /DU [§]
Labenz and Borsch, ³⁵ 1994	Non-randomised	12	GU/DU
Jaspersen et al, ³⁶ 1995	Randomised	12	DU
Rokkas et al, ³⁷ 1995	Randomised	12	DU
Lai et al, ³⁸ 1997	Randomised	53	DU
Macri et al, ³⁹ 1998	Non-randomised	48	DU

* Rebleeding at the time of *H pylori* eradication therapy (No. of patients)

† Rebleeding post-eradication (No. of patients)

‡ GU gastric ulceration

§ DU duodenal ulceration

diagnostic tests have also been shown to be less sensitive than non-biopsy-based methods.³⁰

Drugs such as proton pump inhibitors, which are commonly used to treat bleeding peptic ulcers, can inhibit the activity of *H pylori* and can thus hinder the diagnosis of infection. Simethicone (activated dimethicone), which is commonly used during endoscopic examinations to reduce the formation of air-bubbles, does not affect the sensitivity of the RUT despite the in vitro activity of this drug against *H pylori*.³¹

Long-term outcome for patients with bleeding peptic ulcers

Although most patients with bleeding peptic ulcers recover from the acute bleeding episode, a significant proportion of patients experience a subsequent episode of bleeding. Approximately 30% of patients with bleeding duodenal ulcers and 20% of patients with bleeding gastric ulcers have repeat bleeding in the 2 to 3 years after the first episode.^{32,33}

H pylori eradication and bleeding peptic ulcers that are not associated with the use of non-steroidal anti-inflammatory drugs

Before the recognition of the role of *H pylori* in the pathogenesis of peptic ulcer disease, maintenance therapy with H₂-receptor antagonists was frequently used to prevent recurrent haemorrhage. In a recent placebo-controlled trial, ranitidine was found to significantly reduce the rebleeding rate in instances of bleeding duodenal ulcers.³³ Only 9% of patients receiving ranitidine maintenance therapy had a recurrence of bleeding compared with 36% (12/33) of patients given placebo (mean follow-up period, 61 weeks). However, the disadvantages of such long-term medical therapy include the high cost and the problem of gaining long-term patient compliance. Furthermore, up to 10% of patients still had a recurrence

of bleeding despite the long-term maintenance therapy with H₂-receptor antagonists.³³

The eradication of *H pylori* in patients with uncomplicated peptic ulcers results in ulcer recurrence rates of 0% to 10%.⁸⁻¹¹ Although there is no convincing evidence to suggest that bleeding ulcers are inherently different from non-bleeding ulcers, the role of *H pylori* eradication in the management of bleeding peptic ulcers has been evaluated in a number of studies (Table 1).³⁴⁻³⁷ These randomised and non-randomised studies show unequivocally that the eradication of *H pylori* reduces both the recurrence of ulcers and rebleeding. However, most of these studies had a follow-up time of only 1 year. In a prospective follow-up study of 90 consecutive patients with bleeding gastric ulcers, the cumulative recurrence rate after 2, 5, and 8 years was shown to be 10%, 19%, and 33%, respectively.^{32,33} Recently, one randomised study and one non-randomised study, in which the follow-up was longer than 4 years, have shown that patients without *H pylori* infection rebleed less often than those with persistent *H pylori* infection.^{38,39}

Two randomised studies that compared the efficacy of *H pylori* eradication with maintenance H₂-receptor antagonist therapy in preventing the recurrence of bleeding peptic ulcers, found that *H pylori* eradication was more effective (Table 2).^{40,41} Hence, it seems that, as with uncomplicated peptic ulcers, *H pylori* plays a major aetiological role in the development of bleeding peptic ulcers. It has been estimated that only three to four patients need to be treated for *H pylori* infection to prevent one duodenal ulcer rebleeding.⁴²

H pylori eradication and bleeding peptic ulcers in users of non-steroidal anti-inflammatory drugs

Although the eradication of *H pylori* substantially reduces the rate of recurrence of peptic ulceration

No. of patients Eradication therapy?		Rebleeding* Eradication therapy?		Rebleeding† <i>H pylori</i> present?		P value
Yes	No	Yes	No	Yes	No	
17	14	0/17	4/14	-	-	<0.05
66	0	-	-	0/42	9/24	<0.05
29	22	0/29	6/22	-	-	<0.05
16	15	0/16	6/15	-	-	<0.05
60	60	-	-	2/41	16/55	<0.05
32	0	-	-	0/21	9/11	<0.05

Table 2. *H pylori* therapy and rebleeding: eradication therapy versus long-term maintenance therapy

Study	Study design	Length of follow-up (months)	Ulcer type	No. of patients	No. of patients with rebleeding		P value
Riemann et al. ⁴⁰ 1997	Randomised	24	GU*/DU [†]	95	2/47	4/48	ns
Sung et al. ⁴¹ 1997	Randomised	12	GU/DU	247	0/126	3/121	ns

* GU gastric ulceration

† DU duodenal ulceration

ns not significant

among patients not taking NSAIDs, eradication treatment fails to prevent the development of new peptic ulcers⁴³ and the recurrence of uncomplicated peptic ulcers among patients using continuous therapy of NSAIDs.^{44,45} In contrast, a study has shown that the eradication of *H pylori* reduces the development of peptic ulcers in subjects who are about to start a course of NSAIDs.⁴⁶ In this study, 26% of patients with persistent *H pylori* infection developed ulcers after starting NSAID treatment, compared with only 3% of patients in whom the organism had been successfully eliminated.⁴⁶ These findings suggest that *H pylori* eradication therapy may be more beneficial for patients who are not previous NSAID users and are about to start NSAID treatment.

Only one published study has specifically investigated the effect of eradicating *H pylori* in patients with bleeding peptic ulcers.⁴⁷ *Helicobacter pylori* eradication was found to be ineffective compared with omeprazole treatment in preventing recurrent ulcer bleeding. Only 2% (1/46) of patients who received omeprazole maintenance therapy rebled, whereas 20% (8/41) of patients who received anti-*H pylori* therapy rebled.⁴⁷ It seems likely that NSAID use is more important than *H pylori* infection as a risk factor for the development of mucosal injury and ulceration.

Management of bleeding peptic ulcers that are not associated with the use of non-steroidal anti-inflammatory drugs

The prevalence of *H pylori* is lower in patients with bleeding peptic ulcers than in those with uncomplicated peptic ulcers; hence, it is important to test for the presence of *H pylori* before eradication therapy is started in these patients. It is unsafe to treat all non-users of NSAIDs who have bleeding peptic ulcers with anti-*H pylori* therapy and then to stop all preventive treatment afterwards, because those without *H pylori* infection will have a high risk of rebleeding if long-term antisecretory treatment is not maintained.

The RUT (eg the CLO [*Campylobacter*-like organism] test; Delta West Pty. Ltd., Bentley, Australia)

is most often used to detect *H pylori* at the time of endoscopy because of its short detection time. However, because of the reduced sensitivity of the RUT when the sample is from a bleeding peptic ulcer, other tests such as histological examination or the urea breath test may be required to document the presence of the bacterium. Patients with confirmed *H pylori* infection should receive eradication therapy, whereas patients without infection would probably require maintenance therapy with H₂-receptor antagonists (full-dose rather than half-dose may be required) to reduce the risk of rebleeding.^{33,48}

For *H pylori*-related bleeding peptic ulcers, therapies with very high eradication rates (>90%) are generally preferred because failed eradication (and reinfection) accounts for most cases of rebleeding.^{35,38,39} Treatment usually includes 1 week of triple therapy with a proton pump inhibitor, clarithromycin, and either metronidazole or amoxycillin. Although no clinical studies have assessed whether 1 to 2 weeks' eradication therapy is sufficient for bleeding peptic ulcers, it is reasonable to continue treatment with an ulcer-healing drug such as an H₂-antagonist for a further 4 to 6 weeks after the bacterium has been eliminated. This regimen will allow the complete healing of the complicated ulcer before the *H pylori* status can be reassessed. In one study, more than 10% of patients who had received 1 week of *H pylori*-eradicating drugs (bismuth-based triple therapy with ranitidine) had unhealed ulcers after 6 weeks without an ulcer-healing drug.⁴¹ Maintenance therapy with proton pump inhibitors or sucralfate should not be given, however, since these drugs can suppress *H pylori* activity and consequently give false negative results.

The elimination of *H pylori* should be confirmed after treatment because the risk of rebleeding remains high in patients who fail treatment. For those with a bleeding gastric ulcer, it is recommended that endoscopy should be performed at least 4 weeks after eradication therapy to confirm the successful elimination of *H pylori* and to exclude the presence of a malignant tumour in cases of an unhealed gastric ulcer. For those with duodenal ulcer bleeding, *H pylori* eradication can

be confirmed using non-invasive methods such as the urea breath test, which is simpler and less expensive than endoscopic confirmation. Once *H pylori* eradication is confirmed, it seems justified, given the significantly reduced rebleeding rate post-treatment, that maintenance antisecretory drugs can be discontinued (Table 1). A recent study has confirmed that maintenance antisecretory treatment is not necessary after the eradication of *H pylori*.⁴⁹ In contrast, long-term therapy with H₂-receptor antagonists should be given to patients who fail eradication treatment. This measure may become more important in some regions of Asia where antibiotic resistance to *H pylori* is increasing. Since reinfection also accounts for a significant proportion of rebleeding, maintenance therapy may be considered for patients in areas where reinfection is common; further studies, however, are required.

Managing bleeding peptic ulcers in users of non-steroidal anti-inflammatory drugs

The best intervention for users of NSAIDs who have a bleeding peptic ulcer is to avoid taking NSAIDs. If a patient has a concomitant *H pylori* infection, anti-*H pylori* therapy should be attempted, since it is not possible to determine whether the ulcer is caused primarily by the NSAIDs or by the infection. If *H pylori* is the primary cause, rebleeding would still occur after the discontinuation of NSAID treatment.

If patients with bleeding ulcers must continue using NSAIDs, the lowest possible dose of NSAIDs and the least gastrototoxic NSAIDs such as ibuprofen should be used.⁵⁰ Prophylactic therapy with either misoprostol or omeprazole should also be given if the use of NSAIDs is continued. Misoprostol has been shown to reduce the development of new peptic ulcers in patients taking NSAIDs⁵¹; serious ulcer complications have also been shown to be reduced significantly by this drug, although the decreased risk for ulcer bleeding was not statistically significant.²⁵ Recently, omeprazole has been found to be effective in preventing peptic ulcer recurrence caused by NSAIDs.⁵²⁻⁵⁴ For reasons mentioned above, patients with concomitant *H pylori* infection should be given eradication therapy, although some studies have demonstrated that eliminating the organism does not prevent ulcer recurrence or bleeding complications.⁴³⁻⁴⁵

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